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EXAMINER	
ZISKA, S	
ART UNIT	**PAPER NUMBER**
1804	7

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1804

DATE MAILED: 11/22/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9/8/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 15-22 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-14 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 15-22 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 15-22 are active and examined in this Office Action.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 15 is rejected under 35 U.S.C. § 102(b) as being anticipated by Wilson (WO 87/04462). Wilson discloses vectors useful in a method for preparing a glutamine independent cell line (page 11, fourth paragraph). Wilson discloses vectors containing the glutamine synthetase gene (Abstract)and a gene encoding a heterologous protein operably linked to promoters and that the vectors are useful for the co-amplification of non-selected genes (page 9, bottom paragraph and page 10, fourth full paragraph).Wilson further discloses that the vectors can be used to endow a cell line with the ability to survive in a medium lacking glutamine by transforming a host cell completely lacking or reduced in GS activity with the vector containing the GS gene and that the procedure is particularly, but not exclusively, applicable to myeloma cells (page 11,fourth paragraph). Therefore, the reference anticipates the claims.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the

> time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 16-22 are rejected under 35 U.S.C. § 103 as being unpatentable over Wilson as applied to claim 15 above and further in view of Ringold (USPN 4,656,134) and Foecking. Claim 15 was rejected under 35 U.S.C. 102(b) for reasons as stated above. Wilson differs from the claims in that the reference fails to disclose use of different strength promoters. However, the secondary references, Ringold and Foecking, cure the deficiency. Foecking discloses the hCMV promoter, known in the art to be a very powerful promoter. Regarding claims 16, 18, 21 and 22, Ringold discloses multiple genes linked in tandem arrangement, that the genes would probably be transcribed in the same direction, although transcription may occur from promoters and genes oriented in the opposite direction, and that the selectable gene is upstream of the heterologous genes (column 3, lines 7-34).

Wilson discloses making glutamine independent cell lines on pages 11 and 12 wherein it is stated:

"It has been found that the density to which certain cells, in particular myeloma cells, can grow in a medium may be limited by the requirement for glutamine or by-products of glutamine metabolism. If the cells could be made glutamine independent either directly or as a result of additional medium alterations, it is believed that greater cell densities in culture could be achieved, thereby increasing the amount of protein produced per culture volume by the cell line. It is therefore believed that the use of recombinant DNA sequences encoding GS, for instances in vectors for co-amplification, will lead to highly flexible and advantageous systems which will be surprisingly superior to other similar systems...".

Thus, Wilson clearly suggests producing glutamine independent myeloma cells by co-amplification, selection or transformation using the GS gene. IT would have been obvious to one of ordinary skill to modify the vector of Wilson by using different strength promoters in view of the teachings of Ringold, specifically teaching the advantages of having the weaker promoter direct the expression of the selectable marker and the stronger promoters direct the expression of the heterologous gene. The choice of promoters is a choice amongst equivalents since many are known in the art and readily available. One of ordinary skill would choose the promoter having the desired characteristics and giving the desired level of expression. Choice of promoters is an optimization of routine experimental procedure and one of ordinary skill would be able to pick the promoter giving any desired level of expression, lacking evidence to the contrary.

Regarding claims 16-22,Wilson discloses the use of a vector containing genes encoding the glutamine synthetase (GS)enzyme and encoding a heterologous protein, tPA (page 23, top paragraph). Further, the use of a single vector with both the GS gene and the heterologous gene or the use of a single vector containing each gene alone to transform the cells is clearly contemplated by

Ringold. Wilson discloses vectors having the GS and tPA transcription units in tandem on the same plasmid (page 23, top paragraph).

Regarding claims 20-22, Ringold discloses that immunoglobulin heavy and light chains may be produced according to his method (column 2, lines 67 and 68). Note that the use of the system to produce immunoglobulin heavy and light chains is further rendered obvious by Ringold since Ringold discloses that (column 1, lines 54-59) that more than one heterologous gene may be present downstream of the amplified gene.

Regarding claims 16-22, Ringold discloses use of weak promoters and strong promoters. Ringold specifically states in column 3, lines 35-48, "...the promoter for the amplifiable gene should be weaker than the promoters for the succeeding genes" wherein the succeeding genes are heterologous proteins. Thus, in view of the fact that the amplifiable gene (GS) would have the weaker promoter, protein synthesis would be preferentially directed to the production of the heterologous protein since the gene encoding the heterologous protein would have the stronger promoter. Ringold specifically states "Desirably, the promoter should be at least about 1.5 times, more preferably at least two times as strong (as defined above) for the succeeding genes as compared to the promoter for the amplifiable gene". The succeeding genes are the heterologous genes.

Accordingly, the modification of vector of Wilson by using different strength promoters as suggested by Ringold and Foecking in order to obtain a vector for preparing a cell line was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as

evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800